What Is An IND?

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Regulation

- The regulations in 21 CFR 312 cover procedures and requirements for Investigational New Drug Applications (INDs)
- These regulations define the roles and responsibilities of FDA reviewers, IND sponsors, and clinical investigators

Definitions

Sponsor

- A sponsor is an individual, company, institution, or organization that takes responsibility for and initiates a clinical study (21 CFR 312.3(b), 312.50)

Sponsor

A sponsor is responsible for:

- Selecting qualified investigators
- Ensuring study monitoring
- Maintaining an effective IND, and
- Ensuring AE risk information is provided to the FDA and investigators

Definitions

Investigator

- An investigator is an individual under whose immediate direction the study drug is administered or dispensed. If a team is involved, the leader is the investigator; other team members are sub-investigators

  (21 CFR 312(b), 312.60)

Investigator

An investigator is responsible for:

- Ensuring the study is conducted according to the plan
- Protecting the rights, safety and welfare of subjects, and
- Control of drug under investigation

Definitions

Sponsor-Investigator

- A sponsor-investigator is an individual who both initiates and conducts a study and under whose immediate direction the study drug is administered or dispensed. This person must follow the requirements pertaining to a sponsor and those pertaining to an investigator

  (21 CFR 312(b))

The primary concern during all phases of clinical study is the safety and rights of study subjects

IND Requirements

Even FDA-licensed products are subject to IND regulations if not used under conditions of licensure (“an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice” 21 CFR 312.3(b))

IND Requirements (cont'd)

- For a lawfully marketed product, no IND submission is required if three specific conditions apply (21 CFR 312.2)
  - The study is not intended to support a new indication or labeling change
  - The study does not intend to support a change in advertising
  - The study does not involve a route, dosage or patient population, etc. that increases risk

NOTE!

- The FDA may be aware of other studies that may affect evaluation of potential risk, and
- the FDA is subject to confidentiality requirements and by law can not share this specific information with others

IND Content Requirements 21 CFR 312.23

- Format pertains to all sponsors and sponsor-investigators and fosters efficient review
  - Cover Sheet (and Form FDA 1571)
  - Table of Contents
  - Introductory Statement and General Investigational Plan
  - Clinical Protocol
  - Chemistry, Manufacturing and Control (CMC) Information
  - Pharmacology and Toxicology Information
  - Previous Human Experience
  - Additional Information

Introductory Content Elements

- Cover Sheet (Form FDA 1571)
- Table of Contents
- Introductory Statement (description of product, formulation, route, broad study objectives, relevant previous use, foreign experience)
- General Investigational Plan (rationale, indication, general approach, anticipated studies including number of subjects and possible risks)

Investigator's Brochure (IB)

- Sponsor must provide to all clinical investigators, not required for sponsor investigators (21 CFR 312.55). It must include:
  - Brief product description
  - Pharm/tox summaries
  - Previous human experience
  - Description of anticipated risk and any special monitoring needs
  - Updates as appropriate

Clinical Protocol

The clinical protocol must contain the following elements:

- A statement of objectives
- Investigator, subinvestigator, site and IRB information
- Inclusion/Exclusion criteria
- Study size and design
- Dosage information
- Monitored parameters
- Clinical procedures and lab tests

CMC Information

- Emphasis in Phase I is on identification and control of raw materials and new drug substance, including information on any placebo as well
- Even for Phase I, need enough information to assess safety
- Extent of expected information increases as drug development proceeds
- Throughout product development, good documentation of all manufacturing and testing steps is essential
- Deficiencies in CMC information can result in clinical hold

Pharm/Tox Information

- Animal studies may be conducted to obtain proof of concept or tox information
- Studies should support proposed clinical dose and regimen
- Best to get CBER concurrence on pivotal tox protocols prior to initiation
- Need to submit complete study reports for tox studies, including summary and individual animal data

Other IND Items

- Previous human experience needs to be included (if applicable)
- Additional information such as pre-IND meeting minutes or critical references should be included as well
- Serial numbering of pages of an IND is required (21 CFR 312.23(11)(e)) as this facilitates reference if the FDA has questions

IND Protocol Amendments

21 CFR 312.30

- A new protocol
- Safety or design related changes to an existing protocol
- New investigator (notification is required within 30 days of being added)
- These should be submitted to the FDA prior to implementation
- IRB approval is needed prior to implementation

IND Information Amendments

21 CFR 312.31

Information amendments advise the FDA of:

- New tox, CMC or other technical information
- Notice of discontinuance of a clinical study

Annual Reports

21 CFR 312.33

- To be submitted within 60 days of the anniversary of “in effect” date
- Include enrollment, demographic and conduct status information for each study
- Adverse event summaries (safety reports, deaths, dropouts)
- Drug action information
- Preclinical study status information

Annual Reports (cont'd)

- CMC change information
- Revised/updated investigator brochure with revisions described
- Foreign marketing experience
- Outstanding business with the FDA

Annual Reporting of Adverse Events

RECOMMENDATIONS

- For solicited events – tabulate by study, study group and severity
- For unsolicited events use a line listing by study
- SAEs should be highlighted and discussed
- Include numerators and denominators
- Include cumulative cross-study, multi-year summaries
- Include all events regardless of attribution of relatedness to study drug

Specific Responsibilities of Sponsors

- Selecting qualified investigators and monitors (21 CFR 312.53)
- Obtaining investigator information (signed Form FDA 1572 and CV)
- Controlling shipment of drug – only to participating investigators
- Obtaining clinical protocol information
- Obtaining financial disclosure information
- Providing each investigator an investigator brochure (21 CFR 312.55)
- Informing investigators of new safety observations (see 21 CFR 312.32 on IND safety reports)

Specific Responsibilities of Sponsors

- Review ongoing investigations (21 CFR 312.56)
- Monitor study progress for compliance with protocol
- Dealing with noncompliant investigators
- Review and report to FDA safety and effectiveness data (annual reports and IND safety reports)
- Discontinuance of unsafe investigations and informing the FDA, IRBs and investigators of these actions

Specific Responsibilities of Sponsors

- Maintenance of adequate records (21 CFR 312.57) including:
  - Tracking of drug shipment and information
  - Recording financial interest of investigators
  - Keeping records for 2 years post approval or post last IND drug shipment
  - Retention of reserve samples and standards for certain tests
- Providing FDA with records upon request (21 CFR 312.58)
- Proper disposition of unused investigational drug (21 CFR 312.59)

Specific Responsibilities of Investigators

- Control administration of investigational drug (21 CFR 312.61)
- Provide qualification and study conduct information to sponsor
- Following the protocol (commitment to this required per Form FDA 1572)
- Maintenance of records (21 CFR 312.62) including:
  - Drug disposition
  - Case histories (CRFs, ICFs, medical records)
  - Keeping records for 2 years post approval or post study discontinuation

Specific Responsibilities of Investigators

- Reports to sponsor (21 CFR 312.64)
  - Providing progress reports for IND annual report
  - Promptly reporting safety concerns
  - Provision of final report after study completion
  - Providing financial disclosure information
- Assuring IRB review (21 CFR 312.66)
- Providing FDA with records upon request (21 CFR 312.68)